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09/730,174	12/05/2000	Richard J. Zahradnik	IMUNE-001A	8045

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EXAMINER
HUYNH, PHUONG N

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 09/730,174	Applicant(s) ZAHRADNIK ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7-10,15-17,19 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5, 7-10, 15-17, 19 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 5, 7-10, 15-17, 19 and 24 are pending.

2. In view of the amendment filed 12/27/02, the following objection and rejections remain.

3. The drawings, filed 12/5/00, stand not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 5 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for producing an antibody to the N-terminal portion of (1-84) PTH useful in the determination of intact PTH 1-84 levels in a biological sample, the method comprising the steps: a) administering a first peptide antigen to a host animal to induce antibody production against said first peptide antigen in said host animal, said first peptide antigen being selected from the group consisting of SEQ ID NO: 3-6, (1-34) PTH and (1-84) PTH; b) monitoring antibody titer produced by said administration of said antigen to said host animal; c) extracting antisera produced in said host animal by said host animal; d) isolating and selecting at eat one antibody from said antisera extracted in step c) by affinity chromatography utilizing a second peptide antigen selected from the group consisting of SEQ ID NO: 3-6; (2) the said method wherein said host animal is selected from the group consisting of mice, rabbits and at least one goat; (3) the said method wherein the (1-3) PTH or (1-84) PTH is selected from the group consisting of humans, rats, mice, bovines, dogs, and pigs; (4) the said method wherein said first peptide in step a) has a carrier protein coupled therewith and (5) a test kit and analytical procedures used for determination of bioactive intact PTH utilizing the antibody produced by said method, **does not** reasonably provide enablement for a method as set forth in claim 9 wherein in step a) said at least one peptide antigen "**comprises**" a formula selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6 for PTH detection assay. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of producing antibodies that bind specifically to SEQ ID NOS: 3-6 by immunizing a host with a peptide selected from the group consisting of SEQ ID NO: 3-6, a peptide consisting of amino acid residues 1-34 of human PTH, or a full length parathyroid hormone from humans, rats, mice, bovines, dogs and pigs as depicted in Figures 1 and 2 for PTH binding assays.

The specification does not teach how to make *any* antibody for the claimed method because the term "comprising" in claim 19 is open-ended. It expands the peptide antigen to include additional amino acids at either or both ends. There is insufficient guidance as to structure of the peptide antigen having the undisclosed amino acids. Further, there are no working example in the specification to demonstrate that immunizing a host with *any* undisclosed peptide antigen would generate antibody that binds **specifically** to a second peptide antigen such as SEQ ID NO: 3-6 (that are fragments of PTH).

Kuby *et al*, of record, teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed amino acids that can be added, it is unpredictable which undisclosed peptide antigen would be useful for any purpose.

Colman *et al*, of record, teach that even a single amino acid changes within the interface of an antibody-antigen can raise or lower the affinity of the antibody (See page 33, in particular).

Abaza *et al*, of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the indefinite number of undisclosed amino

acid sequence to be added to the first peptide antigen (without the specific structure such as the specific amino acid residues), it is unpredictable which undisclosed peptide antigen would produce antibody that binds specifically to a peptide selected form the group consisting of SEQ ID NO: 3-6 for the claimed method.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 12/27/02 have been fully considered but are not found persuasive.

Applicants' position is that the claims have been amended and the claimed methods are directed to a very discrete and limited amino acid sequences and do not encompass any peptide antigens.

In respond to Applicant's arguments, amended claim 19 still recites peptide antigen comprise a formula selected from the group consisting of SEQ ID NO: 3-6. The specification does not teach how to make *any* antibody using any peptide antigen, much less for detecting intact PTH (1-84) and having minimal activity to PTH 7-84 or binds to any peptide such as SEQ ID NO: 3-6 because the term "comprising" is open-ended. It expands the peptide antigen to include additional amino acids at either or both ends. There is insufficient guidance as to structure of the peptide antigen having the extra undisclosed amino acids. Further, there are no working example in the specification to demonstrate that immunizing a host with *any* undisclosed peptide antigen would generate antibody that binds **specifically** to a second peptide antigen such as SEQ ID NO: 3-6 (that are fragments of PTH), let alone having minimal activity to PTH 7-84.

6. Claims 5 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method as set forth in claim 9 wherein in step a), said at least one peptide antigen "**comprises**" a formula selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6 for PTH detection assay.

The specification discloses only a method of producing antibodies that bind specifically to SEQ ID NOS: 3-6 by immunizing a host with a peptide selected from the group consisting of SEQ ID NO: 3-6, a peptide consisting of amino acid residues 1-34 of human PTH, or a full length parathyroid hormone from humans, rats, mice, bovines, dogs or pigs as depicted in Figures 1 and 2 for PTH binding assays.

Other than the specific first peptide antigens mentioned above for a method of producing antibodies useful in the determination of bioactive PTH levels in a biological sample, there is inadequate written description about the structure of any first peptide antigen "**comprises**" a formula selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6 because the term "comprising" in claim 19 is open-ended. It expands the peptide antigen to include additional amino acids at either or both ends.

Further, given the lack of a written description of *any* additional representative species of first peptide antigen other than SEQ IN NO: 3-6, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 12/27/02 have been fully considered but are not found persuasive.

Applicants' position is that claims have been amended and the claimed methods are directed to a very discrete and limited amino acid sequences and do not encompass any peptide antigens.

In respond to Applicant's arguments, amended claim 19 still recites peptide antigen comprise a formula selected from the group consisting of SEQ ID NO: 3-6. The specification does not teach how to make *any* antibody for the claimed method because the term "comprising" is open-ended. It expands the peptide antigen to include additional amino acids at either or both ends. There is insufficient guidance as to structure of the peptide antigen having the extra undisclosed amino acids. Further, there are no working example in the specification to demonstrate that immunizing a host with *any* undisclosed peptide antigen would generate antibody that binds **specifically** to a second peptide antigen such as SEQ ID NO: 3-6 (that are fragments of PTH).

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 5, 7, 9, 15, 16, 19 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 4,341,755 (of record, July 1982, PTO 892).

The '755 patent teaches a method for producing antibodies useful for determining intact human or bovine PTH levels comprising the steps of administering at least a first peptide antigen such as human PTH wherein the peptide is within the range about 65-84 to a host animal such as chicken to induce antibody production against the reference first peptide in said host animal, monitoring antibody titer produced by said host animal and isolating antisera produced by said host (See entire document, column 7, lines 19-23, in particular). The reference antibody is capable of binding to a second peptide antigen such as intact human PTH which comprises the claimed formula of SEQ ID NO: 3 (See column 7, line 22, in particular), or intact bovine PTH having or comprising the claimed formula of SEQ ID NO: 6 (See column 7, line 33, in particular) or rat PTH comprising the claimed formula of SEQ ID NO: 5 (See column 7, line 39, in particular). The '755 patent teaches the antibodies can be raised in rabbits and other animals (See column 8, lines 65-66, in particular). The reference peptide antigen is within the range about 65-84 of bovine or human PTH is labeled such as I-125 (See column 7, line 48-50, column 9, lines 47-53, in particular). The '755 patent further teaches that the reference antibodies are useful in a kits for determining bioactive intact PTH (See column 8, line 61-63, Claims of '755, in particular). The term "comprises" is open-ended. It expands the claimed peptide antigen to

include the reference peptide antigen. The claimed antibodies having "minimal reactivity to PTH 7-84" would include the reference antibodies because the claimed antibodies still bind albeit to a less extend. Given that the claimed peptide antigen appears to be the same as that of the reference peptide antigen and since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F 2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

Applicants' position is that (1) the claims have been amended. (2) the claimed method for producing an antibody for detecting intact 1-84 PTH while having minimal reactivity to 7-84 PTH by administering a first peptide antigen selected from the group consisting of SEQ ID NO: 3-6, (1-34)PTH and (1-84)PTH, and the selected antibodies binds to a second peptide antigen selected from the group consisting of SEQ NO 3-6. (3) The reference antibodies are not directed against the extreme N-terminal amino acids of PTH and much less directed against the specific sequence of SEQ ID NO: 3-6. (4) The same could not be utilized in applications to distinguish between intact (1-84)PTH and the (7-84)PTH fragments.

In respond to Applicants' arguments, the term "comprising" in open-end. It expands the first peptide antigen to include additional amino acids at either or both ends to read on the reference peptide antigen such as human recombinant rP1-34. Further, the reference antigen peptide is within about 65-84 of human or bovine PTH (See column 7, lines 48-50, in particular) which would include the claimed antigen peptide. The '755 patent further teaches the reference antibodies are useful in a kit for detecting intact (1-84) PTH (See column 8, line 61-63, Claims of '755, in particular).

In respond to Applicants' arguments that the claimed antibodies have minimal reactivity to 7-84PTH, the limitation "having minimal ractivity to 7-84PTH" has no support in the specification as filed. Further, the claimed antibodies having "minimal reactivity to PTH 7-84" would include the reference antibodies because the claimed antibodies still bind PTH albeit to a less extend

In respond to Applicants' arguments that the claimed antibodies bind to SEQ ID NO: 3-6, the term "comprising" in open-end It expands the first peptide antigen to include additional amino acids at either or both ends to read on the reference peptide antigen. Given that the first peptide antigen appears to be the same as the prior art, and since the Patent Office does not have

the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). In the absence of a side by side comparison, the rejection is maintain for reasons of record.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 5 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 4,341,755 (of record, July 1982, PTO 892) in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 92-94, pages 323-358).

The teachings of the '755 patent have been discussed supra.

The claimed invention in claim 8 differs from the teachings of the reference only that the method wherein the host animal is a goat.

The claimed invention in claim 10 differs from the teachings of the reference only that the method wherein the antibody further includes a label covalently attached thereto said label being selected from the group consisting of radioactive, fluorescent, enzymatic and dye tracers.

Harlow *et al* teach a method of producing polyclonal and monoclonal antibody and the choice of animal such as goat, rabbit, mice for immunization is determined by (1) the amount of serum desired, (2) the evolutionary distance between the species from which the antigen is

isolated, and (3) how much antigen is available (See page 93, in particular). Harlow *et al* teach that immunizing a host animal such as sheep (goat) give large volumes of sera (See page 93, in particular) and the antigens such as PTH derived from human, mice, rat, bovine and dog are evolutionary distant from sheep (See page 93, in particular). Harlow *et al* further teach a method of labeling any antibody such as radioactive iodine, enzyme such as peroxidase, alkaline phosphatase, fluorochrome such as flourescein, rhodamine, Texas red and dye tracer (See page 323-358, in particular). The advantages of radiolabeling antibody are easy to quantitate, easy to label directly and with high sensitivity while the advantages of enzyme or fluorochromes labeled antibody are long shelf life, and high sensitivity (See page 322, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce polyclonal antibody by immunizing a goat, mice or rabbit as taught by Harlow *et al* with the human PTH within the range of about 65-84 peptide antigen as taught by the '755 patent and covalently attached a label such as radioisotope, fluorescent, enzymatic and dye tracers to said antibody as taught by Harlow *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach immunizing host animal such as sheep (goat) give large volumes of sera (See page 93, in particular) and the antigens such as PTH derived from human, mice, rat, bovine and dog are evolutionary distant from sheep (See page 93, in particular). Harlow *et al* further teach the advantages of radiolabeling antibody are easy to quantitate, easy to label directly and with high sensitivity while the advantages of enzyme or fluorochromes labeled antibody are long shelf life, and high sensitivity (See page 322, in particular). The labeled antibodies are useful for determining PTH levels in biological sample as taught by the '755 patent.

Applicants' arguments filed 12/27/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been amended (2) the claimed method for producing an antibody for detecting intact 1-84 PTH while having minimal reactivity to 7-84 PTH by administering a first peptide antigen selected from the group consisting of SEQ ID NO: 3-6, (1-34)PTH and (1-84)PTH, and the selected antibodies binds to a second peptide antigen selected from the group consisting of SEQ NO: 3-6. (3) the teachings of the reference whether alone or in combination with any of the cited references would not convey to one skilled in the art

the method which an antibody can be derived which is capable of detecting intact (1-84) PTH while having minimal cross-reactivity with (7-84) PTH fragments. (4) One skilled in the art would not motivated to modify Lindall (the '755 patent) directed to the C terminus of PTH to derive Applicants' invention as now claimed.

In respond to Applicants' arguments, the term "comprising" in open-end. It expands the claimed first peptide antigen to include additional amino acids at either or both ends to read on the reference peptide antigen. Further, instant claim 5 also recites (1-84)PTH and instant claim 15 recites that the first peptide antigen is from humans.

In respond to Applicant's arguments that the claimed antibodies detect intact 1-84 PTH while having minimal reactivity to 7-84PTH and binds to SEQ ID NO: 3-6, given that the claimed immunogen appears to be the same as that of the prior art and the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). In the absence of a side by side comparison, the rejection is maintain for reasons of record.

In respond to Applicant's arguments that the claimed antibody is capable of detecting intact (1-84) PTH while having minimal cross-reactivity with (7-84) PTH fragments, the arguments of counsel cannot take the place of objective evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965).

In response to applicants' argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the '755 patent teaches a method of making antibodies to PTH for detection of intact hPTH. Harlow *et al* teach that immunizing host animal such as sheep (goat) give large volumes of sera (See page 93, in particular) and the antigens such as PTH derived from human, mice, rat, bovine and dog are evolutionary distant from sheep (See page 93, in particular). Harlow *et al* further teach the advantages of

radiolabeling antibody are easy to quantitate, easy to label directly and with high sensitivity while the advantages of enzyme or fluorochromes labeled antibody are long shelf life, and high sensitivity (See page 322, in particular). The labeled antibodies are useful for determining PTH levels in biological sample as taught by the '755 patent.

12. Claims 5 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 4,341,755 (July 1982, PTO 892) in view of Heinrich *et al* (J Biol Chem 259(5): 3320-3329, March 1984; PTO 892).

The teachings of the '755 patent have been discussed supra.

The claimed invention in claim 17 differs from the teachings of the reference only that the method wherein the first peptide antigen is (1-84) PTH selected from the group of species consisting of humans, rats, bovines, and pigs.

Heinrich *et al* teach the amino acid sequence of rat parathyroid hormone is highly conserved near the N-terminus among the various species such as bovine, humans, pigs (porcine) (See Abstract, Fig 9, in particular) and this conservation in the NH2 terminus of PTH (+1 to +15) region is consistent with the analyses of synthetic fragments and analogs of PTH that have shown for full biological activity (See page 3328, column 1, second full paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the first peptide antigen as taught by the '755 patent for the intact full length (1-84) PTH from humans, bovine, rats, or porcine as taught by Heinrich *et al* for a method for producing antibodies useful in the determination of PTH levels in a biological sample as taught by the '755 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Heinrich *et al* teach the amino acid sequence of rat parathyroid hormone is highly conserved near the N-terminus among the various species such as bovine, humans, pigs (porcine) (See Abstract, Fig 9, in particular) and this conservation in the NH2 terminus of PTH (+1 to +15) region is consistent with the analyses of synthetic fragments and analogs of PTH that have shown for full biological activity (See page 3328, column 1, second full paragraph, in particular). The '755 patent teaches that antibodies to PTH are useful for determining bioactive intact PTH (See column 8, line 61-63, Claims of '755, in particular).

Applicants' arguments filed 12/27/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the teachings of the reference whether alone or in combination with any of the cited references would not convey to one skilled in the art the method which an antibody can be derived which is capable of detecting intact (1-84) PTH while having minimal cross-reactivity with (7-84) PTH fragments. (2) One skilled in the art would not motivated to modify Lindall (the '755 patent) directed to the C terminus of PTH to derive Applicants' invention as now claimed.

In response to applicants' argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the '755 patent teaches a method of making antibodies to PTH for detection of intact hPTH. Heinrich *et al* teach the amino acid sequence of rat parathyroid hormone is highly conserved near the N-terminus among the various species such as bovine, humans, pigs (porcine) (See Abstract, Fig 9, in particular) and this conservation in the NH2 terminus of PTH (+1 to +15) region is consistent with the analyses of synthetic fragments and analogs of PTH that have shown for full biological activity (See page 3328, column 1, second full paragraph, in particular).

In respond to Applicant's arguments that the claimed antibody is capable of detecting intact (1-84) PTH while having minimal cross-reactivity with (7-84) PTH fragments, the arguments of counsel cannot take the place of objective evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965).

13. The following new grounds of objection and rejection are necessitated by the amendment filed 12/27/02

14. Claim 24 is objected to because "Test kits" should have been "A test kit".

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 5, 7-10, 15-17, 19 and 24 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "having minimal reactivity to PTH 7-84" in Claim 5 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase. Further, the specification discloses on page 13 paragraph bridging page 14 that isolated antibodies will have the specificity for the antigenic region of PTH corresponding to amino acid residue sequences 2-12, 1-12, 2-15, and 1-15 or any combination thereof.

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
March 24, 2003

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
3/24/03